REMARKS

The Office Action dated July 11, 2003 presents the examination of claims 1-3, 6-7, and 10-19. Claim 19 is allowed. Claim 1 is amended. Claim 20 is added. Support for claim 20 is found in the subject matter deleted from claim 1. No new matter is inserted into the application.

Markush Group

The Examiner rejects claims 1, 3, 6, and 11-18 under "judicially created doctrine" for reciting an allegedly improper Markush group. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The rejection is clearly improper and must be withdrawn. Under MPEP § 803.02, Practice re Markush-Type Claims, it is improper for the U.S. Patent and Trademark Office to refuse to examine that which an applicant regards as his invention, unless the subject matter in a claim lacks unity of invention. In re Weber, 580 F.2d 455 (CCPA 1978); In re Haas, 580 F.2d 461 (CCPA 1978). Unity of invention exists where compounds encompassed by the Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. U.S. Pat. & Trademark Off., *Manual Pat. Examining. Proc.* § 803.02 (8th ed. Rev. 1, 2001).

In the instant case, the Examiner asserts that there is not a common structural feature because "a common nucleus among the various derivatives of formula I is absent when a heterocyclic moiety is encompassed within the structure." However, the only Markush group recited in independent claims 1 and 6 is "known active substance having antitumor effect selected from the group consisting of pyrimidine derivatives or, optionally, a pharmaceutically acceptable acid addition salt thereof…." In other words, formula I (a hydroximic acid derivative) does not refer to a Markush group.

The pyrimidine derivatives encompassed by the actual Markush group recited in independent claims 1 and 6 satisfy the two-part test for unity of invention under MPEP § 803.02 because (1) the compounds share the same utility of inhibiting DNA or RNA synthesis and/or translation in cancerous cells, and (2) the compounds share the structural similarity of a pyrimidine group which functions to inhibit the biosynthesis of pyrimidine nucleotides or otherwise interfere with the synthesis and/or function of nucleic acids. See, the specification on page 7, line 12 to page 18, line 2.

Thus, the Markush group recited in independent claims 1 and 6 possesses unity of invention, such that restriction thereof is improper. Withdrawal of the instant rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1, 3, 6, and 11-18 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that the recitation of the term "preferably" in claim 1 renders claim 1 and claims dependent thereon indefinite. In order to overcome this rejection, Applicants delete the "preferably" clause from claim 1 and add new claim 20 directed to the deleted subject matter. Thus, the instant rejection is overcome.

Rejection under 35 U.S.C. § 112, first and second paragraphs

The Examiner rejects claims 1, 2, and 6 under 35 U.S.C. § 112, first and second paragraphs for allegedly lacking enablement and for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner asserts that the scope of the term "pyrimidine derivative" cannot be precisely determined. In particular, the Examiner asserts that the definition of "pyrimidine derivative" covers a vast number of compounds which are not enabled by the specification. Applicants respectfully disagree.

Contrary to the Examiner's assertions, the term "pyrimidine derivative" is well known in the art such that a limited definition thereof in the claim is unnecessary. As evidence thereof, Applicants submit pages 1404 to 1408 of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed. (McGraw-Hill, NY). (Attached hereto as Exhibit 1). On page 1404, the chief characteristics of pyrimidine analogs are described. Fluorouracil, floxuridine, and idoxuridine are listed as examples of halogenated pyrimidines, and cytarabine and gemcitabine are listed on page 1405.

Since the term "pyrimidine derivative" is well known in the art, the recitation thereof in the claims is proper under 35 U.S.C. § 112. Withdrawal of the instant rejection is therefore respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-3, 6, 7, and 10-18 under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter not enabled by the specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically the Examiner asserts that the specification enables compound L and fluorouracil, but not *any* pyrimidine derivative and not *any* hydroximic derivative of formula I. Applicants respectfully disagree.

The Examiner has not established a *prima facie* case of non-enablement. In this regard, enablement is presumed unless the Examiner can make a *prima facie* showing otherwise. In order to make a rejection for lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement. In re Wright, 999 F.2d 1557 (Fed. Cir. 1993). In this case, the Examiner has failed to make any findings of fact or present any evidence tending to show that the claimed invention is not enabled by the specification.

Since the Examiner has failed to make a *prima facie* case of non-enablement, the burden has not shifted to Applicants to rebut a rejection under 35 U.S.C. § 112, first paragraph. For these reasons, the rejection is improper and must be withdrawn.

Conclusion

As the above remarks and/or claim amendments fully address, overcome, render moot, or otherwise accommodate the outstanding rejections in the Office Action, the present application is in

condition for allowance. The Examiner is respectfully requested to issue a Notice of Allowance indicating that claims 1-3, 6-7, and 10-20 are allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

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tumor regression in osteosarcoma and in combination therapy of leukemias and non-Hodgkin's lymphomas. A 6- to 72-hour infusion of relatively large amounts of methotrexate may be employed intermittently (from 250 mg to 7.5 g/m^2 or more), but only when leucovorin rescue is used. Such regimens produce cytotoxic concentrations of drug in the cerebrospinal fluid (CSF) and protect against leukemic meningitis. A typical regimen includes the infusion of methotrexate for 6 hours followed by leucovorin at a dose of 15 mg/m^2 every 6 hours for seven doses, with the goal of rescuing normal cells and thereby preventing toxicity. Other dosage regimens also are used. The administration of methotrexate in high dosage has the potential for serious toxicity and should be performed only by experienced chemotherapists who are able to monitor concentrations of methotrexate in plasma. If methotrexate values measured 48 hours after drug administration are 1 μM or higher, higher doses (100 mg/m^2) of leucovorin must be given until the plasma concentration of methotrexate falls below the toxic threshold of 2×10^{-8} M (Stoller *et al.*, 1977). With appropriate precautions, these schedules are relatively free of toxicity. It is imperative to maintain the output of a large volume of alkaline urine, since methotrexate precipitates in the renal tubules in acidic urine. In the presence of malignant effusions, delayed clearance may cause severe toxicity. In patients who become oliguric, isolated reports suggest that continuous-flow hemodialysis can eliminate methotrexate at a rate approximating 50% of the clearance rate in patients with intact renal function (Wall *et al.*, 1996). Methotrexate in high doses with leucovorin rescue has been studied clinically for many years with promising results in osteosarcoma, childhood leukemia, and non-Hodgkin's lymphoma, although the optimal timing and dose of leucovorin required and the optimal schedule of methotrexate administration remain to be established (Ackland and Schilsky, 1987).

Clinical Toxicities. As previously stated, the primary toxicities of methotrexate affect the bone marrow and the intestinal epithelium. Such patients may be at risk for spontaneous hemorrhage or life-threatening infection, and they may require prophylactic transfusion of platelets and broad-spectrum antibiotics if febrile. Side effects usually disappear within 2 weeks, but prolonged suppression of the bone marrow may occur in patients with compromised renal function who have delayed excretion of the drug. The dosage of methotrexate must be reduced in proportion to any reduction in creatinine clearance.

Additional toxicities of methotrexate include alopecia, dermatitis, interstitial pneumonitis, nephrotoxicity, defective oogenesis or spermatogenesis, abortion, and teratogenesis. Hepatic dysfunction is usually reversible but sometimes leads to cirrhosis after long-term continuous treatment, as in patients with psoriasis. Intrathecal administration of methotrexate often causes meningismus and an inflammatory response in the CSF. Seizures, coma, and death may occur rarely. Leucovorin does not reverse neurotoxicity.

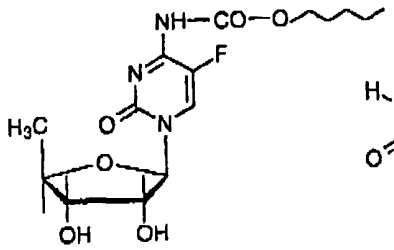
PYRIMIDINE ANALOGS

This class of agents encompasses a diverse and interesting group of drugs that have in common the capacity to inhibit the biosynthesis of pyrimidine nucleotides or to mimic these natural metabolites to such an extent that the analogs interfere with the synthesis or function of nucleic acids. Analogs of deoxycytidine and thymidine have been synthesized as inhibitors of DNA synthesis, and an analog of uracil, 5-fluorouracil, effectively inhibits both RNA function and/or processing and synthesis of thymidylate (*see* Figure 52–8). Drugs in this group have been employed in the treatment of diverse afflictions, including neoplastic diseases, psoriasis, and infections caused by fungi and DNA-containing viruses. The pathways for metabolic activation and degradation of these compounds during systemic administration present opportunities for the development of synergistic combination therapies with other clinically effective drugs.

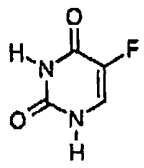
General Mechanism of Action. The best-characterized agents in this class are the halogenated pyrimidines, a group that includes *fluorouracil* (5-fluorouracil, or 5-FU), *floxuridine* (5-fluoro-2′-deoxyuridine, or 5-FUdR), and *idoxuridine* (5-iododeoxyuridine; *see* Chapter 50). If one compares the van der Waals radii of the various 5-position substituents, the dimension of the fluorine atom resembles that of hydrogen, whereas the bromine and iodine atoms are larger and close in size to the methyl group. Thus, idoxuridine behaves as an analog of thymidine, and its primary biological action results from its phosphorylation and ultimate incorporation into DNA in place of thymidylate. In 5-FU, the smaller fluorine at position 5 allows the molecule to mimic uracil biochemically. However, the fluorine-carbon bond is much tighter than that of C—H and prevents the methylation of the 5 position of 5-FU by thymidylate synthase. Instead, in the presence of the physiological cofactor 5,10-methylene tetrahydrofolate, the fluoropyrimidine locks the enzyme in an inhibited state. Thus, substitution of a halogen atom of the correct dimensions can produce a molecule that sufficiently resembles a natural pyrimidine to interact with enzymes of pyrimidine metabolism but at the same time interferes drastically with certain other aspects of pyrimidine action.

A number of 5-FU analogs have reached the clinic. The most important of these is *capecitabine* (N4-pentoxycarbonyl-5′-deoxy-5-fluorocytidine), a drug with proven activity against colon and breast cancers. This orally administered agent is converted to 5′-deoxy-5-fluorocytidine by carboxylesterase activity in liver and other normal and malignant tissues. From that point, it is converted to 5′-deoxy-fluorodeoxyuridine by cytidine deaminase. The final step in its activation occurs when thymidine

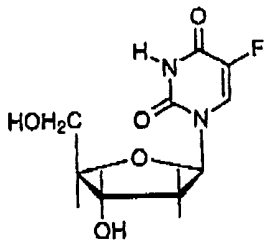
FLUOROPYRIMIDINE ANALOGS



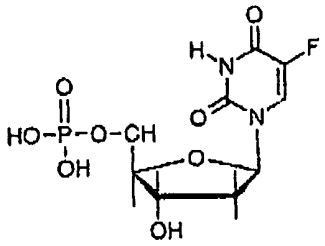
Capecitabine



5-Fluorouracil (5-FU)

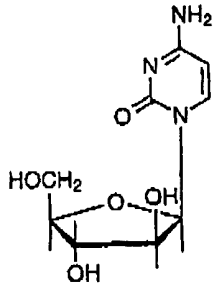


5-Fluorodeoxyuridine (floxuridine)

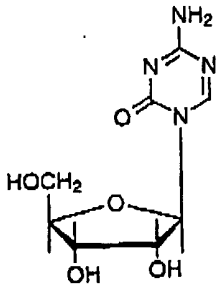


5-Fluorodeoxyuridine monophosphate (active metabolite)

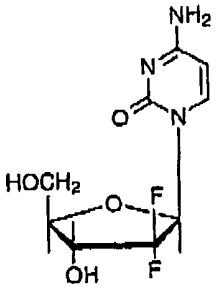
CYTIDINE ANALOGS



Cytosine arabinoside (cytarabine; AraC)



5-Azacytidine



2', 2'-Difluorodeoxycytidine (gemcitabine)

Figure 52–8. Structures of available pyrimidine analogs.

phosphorylase cleaves off the 5′-deoxy sugar, leaving intracellular 5-FU. Tumors with elevated thymidine phosphorylase activity seem particularly susceptible to this drug (Ishikawa *et al.*, 1998).

Nucleotides in RNA and DNA contain ribose and 2′-deoxyribose, respectively. Among the various modifications of the sugar moiety that have been attempted, the replacement of the ribose of cytidine with arabinose has yielded a useful chemotherapeutic agent, *cytarabine* (AraC). As may be seen in Figure 52–8, the hydroxyl group in this molecule is attached to the 2′-carbon in the β, or upward, configuration, as compared with the α, or downward, position of the 2′-hydroxyl in ribose. The arabinose analog is recognized enzymatically as a 2′-deoxyriboside; it is phosphorylated to a nucleoside triphosphate that competes with dCTP for incorporation into DNA (Chabner *et al.*, 2001), where it blocks elongation of the DNA strand and its template function.

Two other cytidine analogs have received extensive clinical evaluation. *5-Azacytidine*, an inhibitor of DNA methylation as well as a cytidine antimetabolite, becomes incorporated predominantly into RNA and has antileukemic as well as differentiating actions *in vitro*. A newer analog, 2′,2′-difluorodeoxycytidine (*gemcitabine*), becomes incorporated into DNA and inhibits the elongation of nascent DNA strands (*see* Figure 52–8). It has promising activity in various human solid tumors, including pancreatic, lung, and ovarian cancer.

Fluorouracil and Floxuridine (Fluorodeoxyuridine)

Mechanism of Action. 5-FU requires enzymatic conversion to the nucleotide (ribosylation and phosphorylation) in order to exert its cytotoxic activity (Figure 52–9). Several routes are available for the formation of the 5′-monophosphate nucleotide (F-UMP) in animal cells. 5-FU may be converted to fluorouridine by uridine phosphorylase and then to F-UMP by uridine kinase, or it may react directly with 5-phosphoribosyl-1-pyrophosphate (PRPP), in a reaction catalyzed by the enzyme orotate phosphoribosyl transferase, to form F-UMP. Many metabolic pathways are available to F-UMP, including incorporation into RNA. A reaction sequence crucial for antineoplastic activity involves reduction of the diphosphate nucleotide by the enzyme ribonucleotide diphosphate reductase to the deoxynucleotide level and the eventual formation of 5-fluoro-2′-deoxyuridine-5′-phosphate (F-dUMP). 5-FU also may be converted directly to the deoxyriboside 5-FUdR by the enzyme thymidine phosphorylase and further to F-dUMP, a potent

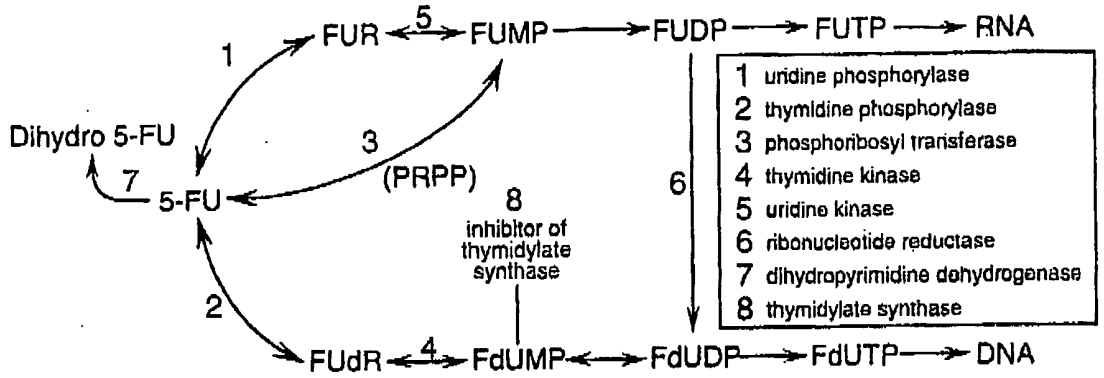
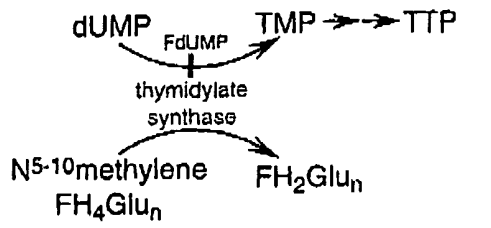


Figure 52–9. Activation pathways for 5-fluorouracil (5-FU) and 5-floxuridine (FUR).

FUDP, floxuridine diphosphate; FUMP, floxuridine monophosphate; FUTP, floxuridine triphosphate; FUdR, fluorodeoxyuridine; FdUDP, fluorodeoxyuridine diphosphate; FdUMP, fluorodeoxyuridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; PRPP, 5-phosphoribosyl-1-pyrophosphate.

inhibitor of thymidylate synthesis, by thymidine kinase. This complex metabolic pathway for the generation of F-dUMP may be bypassed through use of the deoxyribonucleoside of fluorouracil—floxuridine (fluorodeoxyuridine, FUdR)—which is converted directly to F-dUMP by thymidine kinase.

The interaction between F-dUMP and the enzyme thymidylate synthase leads to deletion of TTP, a necessary constituent of DNA (Figure 52–10). The folate cofactor, 5,10-methylenetetrahydrofolate, and F-dUMP form a covalently bound ternary complex with the enzyme. This inhibitory complex resembles the transition state formed during the normal enzymatic reaction when dUMP is converted to thymidylate. Although the physiological complex progresses to the synthesis of thymidylate by transfer of the methylene group and two hydrogen atoms from folate to dUMP, this reaction is blocked in the inhibitory complex by the stability of the fluorine carbon bond on F-dUMP; sustained inhibition of the enzyme results (Santi *et al.*, 1974).



Other Actions of 5-FU nucleotides:

- Inhibition of RNA processing
- Incorporation into DNA

Figure 52–10. Site of action of 5-fluoro-2'-deoxyuridine-5'-phosphate (5-FdUMP).

5-FU, 5-fluorouracil; dUMP, deoxyuridine monophosphate; TMP, thymidine monophosphate; TTP, thymidine triphosphate; FdUMP, fluorodeoxyuridine monophosphate; FH_2Glu_n, dihydrofolate polyglutamate; FH_4Glu_n, tetrahydrofolate polyglutamate

5-FU also is incorporated into both RNA and DNA. In 5-FU–treated cells, both F-dUTP and dUTP (the substrate that accumulates behind the blocked thymidylate synthase reaction) incorporate into DNA in place of the depleted physiological TTP. The significance of the incorporation of F-dUTP and dUTP into DNA is unclear (Canman *et al.*, 1993). Presumably, the incorporation of deoxyuridylate and/or fluorodeoxyuridylate into DNA would call into action the excision–repair process. This process may result in DNA strand breakage because DNA repair requires TTP, but this substrate is lacking as a result of thymidylate synthase inhibition (Mauro *et al.*, 1993). 5-FU incorporation into RNA also causes toxicity as the result of major effects on both the processing and functions of RNA (Armstrong, 1989; Danenberg *et al.*, 1990).

A number of biochemical mechanisms have been identified that are associated with resistance to the cytotoxic effects of 5-FU or floxuridine. These mechanisms include loss or decreased activity of the enzymes necessary for activation of 5-FU, decreased pyrimidine monophosphate kinase (which decreases incorporation into RNA), amplification of thymidylate synthase (Washtein, 1982), and altered thymidylate synthase that is not inhibited by F-dUMP (Barbour *et al.*, 1990). Both experimental studies and clinical trials support the position that the response to 5-FU correlates significantly with low levels of the degradative enzymes, dihydrouracil dehydrogenase and thymidine phosphorylase, and a low level of expression of the target enzyme, thymidylate synthase (van Triest *et al.*, 2000). Recent investigations have demonstrated that the level of thymidylate synthase is finely controlled by an autoregulatory feedback mechanism wherein the thymidylate synthase protein interacts with and controls the translational efficiency of its own messenger RNA. This mechanism provides for the rapid modulation of the level of thymidylate synthase necessary for cellular division and also

Table 52–2
Modulators of Cytotoxic Activity of 5-Fluorouracil (5-FU)

MODULATOR	PURPORTED MECHANISM(S) OF INTERACTION
Cisplatin	Enhanced DNA strand breaks secondary to decreased repair Enhanced thymidylate synthase inhibition
Interferon	Enhanced 5-FU anabolism Decreased "rebound" synthesis of thymidylate synthase
Leucovorin	Enhanced thymidylate synthase inhibition
Methotrexate	Enhanced 5-FU anabolism Enhanced RNA incorporation
PALA*	Enhanced 5-FU anabolism Enhanced RNA incorporation
Uridine	Diminished RNA incorporation (? selective rescue for normal cells)

*PALA, *N*-phosphonoacetyl-L-aspartate.

may be an important mechanism by which malignant cells become rapidly insensitive to the effects of 5-fluorouracil (Chu *et al.*, 1991; Swain *et al.*, 1989). Some malignant cells appear to have insufficient concentrations of 5,10-methylene tetrahydrofolate and, thus, cannot form maximal levels of the inhibited ternary complex with thymidylate synthase. Addition of exogenous folate in the form of 5-formyl-tetrahydrofolate (leucovorin) increases formation of the complex in both laboratory and clinical experiments and has enhanced responses to 5-FU in clinical trials (Ullman *et al.*, 1978; Grogan *et al.*, 1993). Except for inadequate intracellular folate pools, it is not established which (if any) of the other mechanisms is associated with clinical resistance to 5-FU and its derivatives (Grem *et al.*, 1987).

In addition to leucovorin, a number of other agents have been combined with 5-FU in attempts to enhance the cytotoxic activity through biochemical modulation. These agents, along with their proposed mechanisms of interaction, are shown in Table 52–2. The most clinically interesting combinations with 5-FU include methotrexate, interferon, leucovorin, or cisplatin, all of which are currently under investigation to define their ultimate clinical roles. Agents that inhibit early steps in pyrimidine biosynthesis, such as PALA (*N*-phosphonoacetyl-L-aspartate), an inhibitor of aspartate transcarbamylase, provide synergistic interaction with 5-FU in experimental systems, but these combinations have no proven clinical value (Grem *et al.*, 1988). Methotrexate, by inhibiting purine synthesis and increasing cellular pools of PRPP, enhances the activation of 5-FU and increases antitumor activity of 5-FU when given prior to but not following 5-FU. In clinical trials, the combination of cisplatin and 5-FU has yielded impressive responses in tumors of the upper aerodigestive tract, but the molecular basis of their interaction is not well understood (Grem, 2001).

Absorption, Fate, and Excretion. 5-FU and floxuridine are administered parenterally, since absorption after ingestion of the drugs is unpredictable and incomplete. Metabolic degradation occurs in many tissues, particularly the liver. Floxuridine is converted by thymidine or deoxyuridine phosphorylases into 5-FU. 5-FU is inactivated by reduction of the pyrimidine ring; this reaction is carried out by dihydropyrimidine dehydrogenase (DPD), which is found in liver, intestinal mucosa, tumor cells, and other tissues. Inherited deficiency of this enzyme leads to greatly increased sensitivity to the drug (Lu *et al.*, 1993; Milano *et al.*, 1999). The rare individual who totally lacks this enzyme may experience profound drug toxicity following conventional doses of the drug. DPD deficiency can be detected either by enzymatic or molecular assays using peripheral white blood cells, or by determining the plasma ratio of 5-FU to its metabolite, 5-fluoro-5,6-dihydrouracil, which is ultimately degraded to α-fluoro-β-alanine (Heidelberger, 1975; Zhang *et al.*, 1992).

Rapid intravenous administration of 5-FU produces plasma concentrations of 0.1 to 1.0 mM; plasma clearance is rapid ($t_{1/2}$ 10 to 20 minutes). Urinary excretion of a single dose of 5-FU given intravenously amounts to only 5% to 10% in 24 hours. Although the liver contains high concentrations of DPD, dosage does not have to be modified in patients with hepatic dysfunction, presumably because of degradation of the drug at extrahepatic sites or by vast excess of this enzyme in the liver. Given by continuous intravenous infusion for 24 to 120 hours, 5-FU achieves plasma concentrations in the range of 0.5 to 8.0 μM. 5-FU readily enters the CSF, and concentrations greater than 0.01 μM are sustained for up to 12 hours following conventional doses (Grem, 2001).

Capecitabine is well absorbed orally, yielding high plasma concentrations of 5′-deoxy-fluorodeoxyuridine (5′-dFdU), which disappears with a half-life of about 1 hour. 5-FU levels are less than 10% of those of 5′-dFdU. Liver dysfunction delays the conversion of the parent compound to 5′-dFdU and 5-FU, but there is no consistent effect on toxicity (Twelves *et al.*, 1999).

Therapeutic Uses. ***5-Fluorouracil.*** Accumulated experience with 5-FU (ADRUCIL) indicates that the drug produces partial responses in 10% to 20% of patients with metastatic carcinomas of the breast and the gastrointestinal tract; beneficial effects also have been reported in carcinoma of the ovary, cervix, urinary bladder, prostate, pancreas, and oropharyngeal areas. For average-risk patients in good nutritional status with adequate hematopoietic function, the weekly dosage regimen employs 750 mg/m^2 alone or 500 to 600 mg/m^2 with leucovorin once each week for 6 of 8 weeks. Other regimens use daily doses of 500 mg/m^2 for 5 days, repeated in monthly cycles. When used with leucovorin, daily doses of 5-FU must be reduced to 375 to 425 mg/m^2 for 5 days because of mucositis and diarrhea. It also has been given as a continuous infusion for up to 21 days (300 mg/m^2 per day), or as a biweekly 48-hour continuous infusion (de Gramont *et al.*, 1998).

Floxuridine (FUdR). FUdR (fluorodeoxyuridine; FUDR) is used primarily by continuous infusion into the hepatic artery for treatment of metastatic carcinoma of the colon

or following resection of hepatic metastases (Kemeny *et al.*, 1999); the response rate to such infusion is 40% to 50%, or double that observed with intravenous administration. Intrahepatic arterial infusion for 14 to 21 days may be used with minimal systemic toxicity. However, there is a significant risk of biliary sclerosis if this route is used for multiple cycles of therapy (Kemeny *et al.*, 1987; Hohn *et al.*, 1986). Continuous infusion of floxuridine into the arterial blood supply of tumors at other sites, such as in the head and neck region, may provide beneficial clinical effects. With any of these regimens, treatment should be discontinued at the earliest manifestation of toxicity (usually stomatitis or diarrhea) because the maximal effects of bone marrow suppression and gut toxicity will not be evident until days 7 to 14.

***Capecitabine* (XELODA).** Capecitabine is approved by the United States Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in patients who have not responded to a regimen of paclitaxel and an anthracycline antibiotic (*see* below). The recommended dose is 2500 mg/m^2 daily, given orally in two divided doses with food, for 2 weeks followed by a rest period of 1 week. This cycle is then repeated two more times.

Combination Therapy. Higher response rates are seen when 5-FU is used in combination with other agents, such as cyclophosphamide and methotrexate (breast cancer), cisplatin (head and neck cancer), and with leucovorin in colon cancer (*see* Table 52–2). The use of 5-FU in combination regimens has improved survival in the adjuvant treatment for breast cancer (Early Breast Cancer Trialists Collaborative Group, 1988) and, with leucovorin, for colorectal cancer (Wolmark *et al.*, 1993). 5-FU is a potent radiation sensitizer and is being used with concurrent radiotherapy for primary therapy of locally advanced tumors of the head and neck, esophagus, lung, and rectum. 5-FU is used widely with very favorable results for the topical treatment of premalignant keratoses of the skin and multiple superficial basal cell carcinomas. It also is effective in severe recalcitrant psoriasis (Alper *et al.*, 1985).

Clinical Toxicities. The clinical manifestations of toxicity caused by 5-FU and floxuridine are similar and may be difficult to anticipate because of their delayed appearance. The earliest untoward symptoms during a course of therapy are anorexia and nausea; these are followed by stomatitis and diarrhea, which constitute reliable warning signs that a sufficient dose has been administered. Mucosal ulcerations occur throughout the gastrointestinal tract and may lead to fulminant diarrhea, shock, and death, particularly in patients who are receiving continuous infusions of 5-FU or in those receiving 5-FU with leucovorin. The major toxic effects of bolus-dose regimens result from the myelosuppressive action of these drugs. The nadir of leukopenia is usually between days 9 and 14 after the first injection of drug. Thrombocytopenia and anemia also may occur. Loss of hair, occasionally progressing to total alopecia, nail changes, dermatitis, and increased pigmentation and atrophy of the skin may be encountered. Neurological manifestations, including an acute cerebellar syndrome, have been reported, and myelopathy has been observed after the intrathecal administration of 5-FU. Cardiac toxicity, particularly acute chest pain with evidence of ischemia in the electrocardiogram, also may occur. The low therapeutic indices of these agents emphasize the need for very skillful supervision by physicians familiar with the action of the fluorinated pyrimidines and the possible hazards of chemotherapy.

Capecitabine causes much the same spectrum of toxicities as 5-FU (diarrhea, myelosuppression), but also a progressive hand-foot syndrome consisting of erythema, desquamation, pain, and sensitivity to touch of the palms and soles.

Cytarabine (Cytosine Arabinoside; AraC)

Cytarabine (1-β-D-arabinofuranosylcytosine; AraC) is the most important antimetabolite used in the therapy of acute myelocytic leukemia. It is the single most effective agent for induction of remission in this disease (for review, *see* Garcia-Carbonero *et al.*, 2001).

Mechanism of Action. This compound is an analog of 2′-deoxycytidine with the 2′-hydroxyl in a position *trans* to the 3′-hydroxyl of the sugar, as shown in Figure 52–8. The 2′-hydroxyl causes steric hindrance to the rotation of the pyrimidine base around the nucleosidic bond. The bases of polyarabinonucleotides cannot stack normally, as do the bases of polydeoxynucleotides.

AraC penetrates cells by a carrier-mediated process shared by physiological nucleosides. As with most purine and pyrimidine antimetabolites, cytarabine must be "activated" by conversion to the 5′-monophosphate nucleotide (AraCMP), a reaction catalyzed by deoxycytidine kinase. AraCMP can then react with appropriate nucleotide kinases to form the diphosphate and triphosphate nucleotides (AraCDP and AraCTP). AraC competes with the physiological substrate deoxycytidine 5′-triphosphate (dCTP) for incorporation into DNA by DNA polymerases. The incorporated AraCMP residue is a potent inhibitor of DNA polymerase. The effects of AraC on DNA polymerase activity extend not only to DNA chain elongation during semiconservative DNA replication, but also to DNA repair. There is a significant relationship between inhibition of DNA synthesis and the total amount of AraC incorporated into DNA. Thus, incorporation of about five molecules of AraC per 10^4 bases of DNA decreases cellular clonogenicity by about 50%.

AraC also causes an unusual reiteration of DNA segments, thus increasing the possibility of recombination, crossover, and gene amplification. In addition, AraC is converted intracellularly to AraCDP-choline, an analog of the physiological CDP-choline, which inhibits the synthesis of membrane glycoproteins and glycolipids. Furthermore, AraCMP inhibits the transfer of galactose, *N*-acetylglucosamine, and sialic acid to cell-surface glycoproteins, and AraCTP inhibits the synthesis of CMP-